Specification under 35 USC 112, first paragraph, has been withdrawn.

Claims 15-22 and 36-38 are provisionally rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over the claims of pending application Serial No. 07/898,019. As noted, the rejection is provisional and, in any event, subject to disposition through the filing of a timely terminal disclaimer pursuant to 37 CFR 1.321 (b). We note that the applications are commonly owned.

Applicants are prepared to file such a timely terminal disclaimer upon an indication of allowance.

The Examiner has repeated the rejection of claims 36 - 38 on Kaplan, U.S. Patent 4,151,065 and the Maxim/Gilbert and Sanger prior art discussed in the Specification at page 3 in view of Khanna et al., U. S. Patent No. 4,151,065 and Ward, U.S. Patent 4,711,955.

The rejection should be withdrawn. Kaplan relates to a horizontal slab gel electrophoresis apparatus, the tray or trough 30 of which is made of an ultraviolet transmitting material. While Kaplan discloses the separation of DNA fragments on the gel, column 7, lines 29 et seq, there is no suggestion in Kaplan of <u>sequencing</u> the DNA. Kaplan is fundamentally deficient as a primary reference.

The Examiner implies that Kaplan relates to sequencing. It does not. Further, it is never stated in Kaplan what the detectable label is or how it is used. The reliance on Kaplan is completely misplaced.

The Maxim/Gilbert and Sanger prior art is not suggestive of the present invention. As is pointed out in the Specification, in the sequencing according to the Maxim/Gilbert and Sanger methods, radiolabels are used.

Khanna and Ward are not at all pertinent. Khanna et al. disclose a class of di(chalcogen ether) symmetrically substituted fluorescein compounds which are disclosed for conjugation to polypeptides or to solid or soluble supports for use in diagnostic immunoassays. Ward relates to a nucleotide or oligo- or polynucleotide sequence having a 7-deazapurine or a pyrimidine substituent and a moiety selected from the group consisting of biotin and iminobiotin. Neither of these patents is at all pertinent to the present invention and suggest nothing at all in relation to DNA sequencing.

In the practice of the present invention, the reaction mixtures are combined and electrophoresed together. The separated bands of DNA are then detected by their fluorescence and the sequence of their colors directly yields the base sequence. A major result of this fluorescence detection method is that it can readily

be automated. This invention has made it possible to begin to sequence extensive stretches of the human genome, which contains $3x10^9$ base pairs. The prior art method using autoradiograms requires contact with the gel and is too slow to enable full scale analysis of the human genome.

The present invention has been acknowledged and acclaimed by those skilled in the art, see Stryer, "Biochemistry", 3rd Edition, 1988, W.H. Freeman and Company, pp. 120-123, copies attached which states, with reference to the present invention:

> "A fluorescent tag is attached to the oligonucleotide primer - a differently colored one in each of the four chain-terminating reaction mixtures (e.g., a blue emitter for termination at A and a red one for termination at C). The reaction mixtures are combined and electrophoresed together. The separated bands of DNA are then detected by their fluorescence as they pass out the bottom of the tube, and the sequence of their colors directly yields the base sequence (Figure 6-9). Sequences of up to 500 bases can now be determined in this way. An attractive feature of this fluorescence detection method is that it can readily be automated. The sequencing of the entire E. coli genome (3×10^6 base pairs) has now become feasible. We can even begin to think about determining the sequence of extensive stretches of the human genome,

which contains 3 x 10^9 base pairs."

The avoidance of radiolabels is also beneficial from a health and environmental standpoint.

We reiterate that these facts serve to demonstrate that the present invention was not obvious to those skilled in the art for, had the use of colored, fluorescent and similar labels been obvious to use in DNA sequencing, it would have been done long ago. The benefits of using these labels in DNA sequencing are undeniable, and so desirable that everyone would have jumped on the colored label-fluorescent label handwagon many years ago, had it been obvious to do so. These circumstances are powerful evidence that the present invention was not obvious.

The combination of Khanna et al, Ward and Kaplan which is proposed in the Office Action is based on careful selection and amounts to a reconstruction of these three patents (together with Maxim/Gilbert and Sanger) in a way which is suggested only by applicants' Specification. This hindsight reconstruction of the prior art is clearly improper.

The present invention represents a major advance in the art of DNA sequencing.

The present invention clearly satisfies the requirements for

a finding of non-obviousness.

The rejection of claims 36 - 38 on prior art should be withdrawn.

In the absence of more pertinent prior art, the Notice of Allowance is requested.

Respectfully submitted,

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